Blood Pressure Variability and Risk of Heart Failure in ACCORD and the VADT

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OBJECTIVE

Although blood pressure variability is increasingly appreciated as a risk factor for cardiovascular disease, its relationship with heart failure (HF) is less clear. We examined the relationship between blood pressure variability and risk of HF in two cohorts of type 2 diabetes participating in trials of glucose and/or other risk factor management.

RESEARCH DESIGN AND METHODS

Data were drawn from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Veterans Affairs Diabetes Trial (VADT). Coefficient of variation (CV) and average real variability (ARV) were calculated for systolic (SBP) and diastolic blood pressure (DBP) along with maximum and cumulative mean SBP and DBP during both trials.

RESULTS

In ACCORD, CV and ARV of SBP and DBP were associated with increased risk of HF, even after adjusting for other risk factors and mean blood pressure (e.g., CV-SBP: hazard ratio [HR] 1.15, $P = 0.01$; CV-DBP: HR 1.18, $P = 0.003$). In the VADT, DBP variability was associated with increased risk of HF (ARV-DBP: HR 1.16, $P = 0.001$; CV-DBP: HR 1.09, $P = 0.04$). Further, in ACCORD, those with progressively lower baseline blood pressure demonstrated a stepwise increase in risk of HF with higher CV-SBP, ARV-SBP, and CV-DBP. Effects of blood pressure variability were related to dips, not elevations, in blood pressure.

CONCLUSIONS

Blood pressure variability is associated with HF risk in individuals with type 2 diabetes, possibly a consequence of periods of ischemia during diastole. These results may have implications for optimizing blood pressure treatment strategies in those with type 2 diabetes.

In the last decade, visit-to-visit variability in blood pressure has evolved from being regarded as merely a hindrance to proper monitoring of mean blood pressure to being recognized as a potential additional risk factor for cardiovascular disease (CVD) and mortality (1,2). Results from several cohort studies (3–6) reveal that visit-to-visit variability in systolic (SBP) and diastolic blood pressure (DBP) is closely associated with risk of coronary heart disease, stroke, and both cardiovascular and all-cause mortality.

Despite this recent evidence for a role of visit-to-visit blood pressure variability in ischemic cardiovascular events and mortality, inquiry into its role in heart failure (HF), a serious condition with increasing prevalence, is limited (5,7). HF is a common

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comorbidity in patients with type 2 diabetes (8), and among those with HF, the prevalence of concomitant type 2 diabetes rose 3.8% each year from 1979 to 1999 (9). Patients with type 2 diabetes have rates of HF ~2.5-fold higher than individuals without type 2 diabetes (10,11). In light of this mounting public health problem, how visit-to-visit blood pressure variability may influence risk of HF among patients with type 2 diabetes merits careful examination. Exploring this association in the context of aggressive blood pressure lowering is of particular clinical interest. As recent findings suggest that low SBP (7) or DBP (12) may also be linked to adverse cardiovascular outcomes, determining the extent to which blood pressure variability influences HF at different blood pressure levels may be of further prognostic importance.

For these reasons, we examined the relationship between visit-to-visit blood pressure variability and HF using two large cohorts with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Veterans Affairs Diabetes Trial (VADT). These trials have the advantage of frequent and carefully measured blood pressure assessments and adjudicated HF events, rendering them ideal cohorts for this research question.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The ACCORD trial was a double two-by-two factorial, parallel treatment trial in which patients were randomly assigned to receive intensive glucose lowering targeting an HbA_{1c} concentration of $<6.0\%$ or standard treatment targeting an HbA_{1c} of 7.0–7.9%, and to distinct blood pressure and lipid interventions arms. ACCORD included participants with type 2 diabetes, HbA_{1c} concentrations of $\geq 7.5\%$, and who were aged 40–79 years with a history of CVD or 55–79 years with evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity). Of the 10,251 participants in the entire ACCORD population, 4,733 were randomized to two blood pressure intervention arms: an intensive blood pressure arm with a goal of reducing SBP to <120 mmHg or a standard blood pressure arm with a goal of reducing SBP to <140 mmHg. The goal was to determine whether a strategy with a more aggressive blood pressure target would confer a reduction in the rate of CVD events. Blood pressure measurements were available at baseline and at 4-month intervals thereafter in the standard group and at 2-month intervals in the intensive group. Details of the ACCORD trial's overall design (13,14) and the rationale for the blood pressure intervention, including a description of the treatment protocol (15), have been previously reported.

The current post hoc analysis included those who did and did not participate in the blood pressure trial. For consistency among all ACCORD participants, we included in the current analysis only data from the 4-month visits. To reduce the effect of rapid reduction in blood pressure at the early phase of the ACCORD trial on blood pressure variability measures, we excluded blood pressure observations from the baseline visit in this analysis.

The VADT was a randomized trial that enrolled 1,791 U.S. veterans who had a suboptimal response to therapy for type 2 diabetes ($HbA_{1c} > 7.5\%$) to receive intensive or standard glucose control. The design and the principal results have been described previously (16). An established algorithm was followed in which the two groups were treated with similar glucose-lowering medications (but different doses) with a goal of the intensive treatment group of achieving nearly normal glucose control. Other cardiovascular risk factors, including blood pressure, were targeted similarly in both groups to achieve guideline-recommended levels at that time. To reduce the effect of rapid reduction in blood pressure, which occurred during the general risk factor management in the early phase of the trial, we excluded the baseline and 3-month visit blood pressure observations in this analysis. In both cohorts, we also excluded those who had two or fewer blood pressure measurements.

Outcome

New HF was queried at each site visit and defined as "congestive heart failure" death or hospitalization for HF, documented with clinical and radiologic evidence and confirmed by an adjudication committee in ACCORD (13). In the VADT, "congestive heart failure" was characterized by new or worsening HF as determined by clinical questionnaire and physical examination and adjudicated by an end point committee (16). Participants with known HF at baseline were excluded from this analysis.

Blood Pressure Variables

In a comprehensive analysis of the relationships of various blood pressure variability metrics, it was determined that many were significantly correlated and that only one measure of overall variability, such as the SD or coefficient of variation (CV), one measure of variability between consecutive visits (e.g., average real variability [ARV]), and at least one measure of extreme values would adequately characterize blood pressure variability (17). Therefore, we report CV and ARV in this analysis and compare these with the maximum and cumulative mean (average of blood pressure before the event or censor time) of SBP and DBP.

Statistical Analysis

Data are expressed as means (SD) for continuous variables or as numbers and percentages for categorical variables. Differences between patients who did and did not develop an HF event were analyzed using the Wilcoxon test for continuous variables and the χ^2 test or Fisher exact test, as appropriate, for categorical variables. To assess in more detail the role of blood pressure variability in HF, we reported age-adjusted hazard ratios (HRs) for HF across quartiles of CV-SBP, ARV-SBP, CV-DBP, and ARV-DBP in ACCORD.

Cox proportional hazards models were used in both trials to evaluate time-dependent effects of blood pressure measures on HF. HRs for all variables were standardized to a change of 1 SD. The SDs of time-dependent measures were calculated at every time point for all participants and then averaged over all time points. Three models for variability were reported. Model 1 adjusted for age only. Model 2 adjusted for age and covariates reflecting significant baseline differences between those who did and did not develop HF. Model 3 adjusted for model 2 covariates and added the cumulative mean of blood pressure; this model was used to determine whether variability measures provided information beyond standard blood pressure measures.

Because it was previously hypothesized that nonadherence to medications

may explain heretofore reported relationships between blood pressure variability and adverse cardiovascular outcomes (5,18), we conducted sensitivity analyses to determine the extent to which use and adherence to blood pressure medications influences the variability-HF relationship.

Several subgroup analyses in ACCORD were performed. To test whether blood pressure variability confers increased HF risk in the setting of lower blood pressure, we tested these associations after stratifying by baseline SBP (<140 mmHg, <130 mmHg, and <120 mmHg) and baseline DBP (<70 mmHg and <60 mmHg). Because the deleterious relationship of low DBP with myocardial injury in a previous study was only present in individuals with a high pulse pressure (12), we also examined pulse pressure as a covariate in ACCORD.

We also used the cumulative mean of SBP and DBP, rather than baseline blood pressure, as cutoffs in a separate analysis of those with low blood pressure. To determine whether variability above the mean blood pressure (i.e., elevations) or variability below the mean blood pressure (i.e., dips) conferred risk of HF, we calculated areas under the curve of these (hereafter, "variability area"), respectively, and tested for associations with the outcome. Finally, among the individuals with low blood pressure, we assessed the association between blood pressure variability and *1*) HF in those who did and did not report a baseline history of CVD and *2*) myocardial infarction (MI) occurring during the study.

All statistical analyses were performed using R 3.6.1 software (https://www.r-project.org). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

After exclusions for history of HF at baseline and those with too few visits, 9,383 individuals in ACCORD and 1,550 individuals in the VADT were included in this analysis. Mean follow-up time to an HF event or censorship in ACCORD was 56.6 months, and the mean follow-up time in the VADT was 59.5 months. During the study periods, an HF event occurred in 313 individuals in ACCORD and in 102 individuals in the VADT. Supplementary Fig. 1 shows the mean SBP and DBP over the entire study duration in both trials, illustrating the initial drop in blood pressures during the early trial phase.

Blood Pressure Variability and HF in ACCORD

Baseline characteristics among ACCORD participants who did and did not have an HF event are presented in Table 1. Baseline age, sex, race/ethnicity, diabetes duration, history of CVD, smoking history, BMI, DBP, SBP, HDL cholesterol, HbA_{1c}, urine albumin-to-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) differed significantly between those who did and did not have an HF event.

To assess the relationship between blood pressure variation and incident HF in ACCORD, we first determined HRs across quartiles of blood pressure variability (Fig. 1). There was a strong, significant trend of increasing HF risk with increasing quartiles of both SBP and DBP variability.

We then evaluated measures of blood pressure variability, as well as mean and maximum blood pressure, as predictors of HF in ACCORD in adjusted models (Table 2). In age-adjusted models (model 1), mean and maximum SBP, CV-SBP, and ARV-SBP significantly predicted the risk of HF. For DBP measures, only measures of variability (CV-DBP and ARV-DBP) were significant risk factors for HF. All blood pressure measures that were significant predictors in model 1 remained significant after further adjustment for variables that differed between those who did and did not develop an HF event (model 2). To examine whether measures of blood pressure variability provided information beyond standard measures of blood pressure, estimates were further adjusted for cumulative blood pressure means (SBP or DBP) (model 3). While SBP and DBP variability measures remained significant predictors of HF, maximum SBP was no longer significant in model 3. The risk estimates for the measures of blood pressure variability were not appreciably changed after adjustment for pulse pressure (e.g., model 3 + pulse pressure, CV-DBP HR 1.21, $P < 0.001$; ARV-DBP HR 1.19, $P < 0.001$). Additionally, the relationship of blood pressure variability with HF was not stronger in those with a high baseline pulse pressure (>60 mmHg).

Table 1—Baseline characteristics in ACCORD by incident HF status

	No HF (n = 9,070)	HF (n = 313)	P value
Age (years)	62.6 (6.5)	65.5 (6.8)	<0.001
Intensive BP treatment (% yes)	2,105 (23.2)	58 (18.5)	0.06
Female (% yes)	3,507 (38.7)	96 (30.7)	0.005
Race/ethnicity (%)			0.001
White	5,634 (62.1)	217 (69.3)	
Black	1,707 (18.8)	64 (20.4)	
Hispanic	654 (7.2)	15 (4.8)	
Other	1,075 (11.9)	17 (5.4)	
Diabetes duration (years)	10.6 (7.5)	12.8 (8.4)	<0.001
History of CVD (% yes)	2,912 (32.1)	177 (56.5)	<0.001
Smoker† (% yes)	4,034 (51.0)	163 (60.1)	0.004
BMI (kg/m^2)	32.1 (5.4)	33.2 (5.6)	0.001
DBP (mmHg)	75 (10)	73 (11)	<0.001
SBP (mmHg)	136 (17)	139 (19)	0.001
HDL cholesterol (mg/dL)	42 (12)	39 (11)	<0.001
LDL cholesterol (mg/dL)	105 (34)	102 (34)	0.15
Total cholesterol (mg/dL)	183 (42)	179 (41)	0.06
Triglycerides (mg/dL)	190 (150)	197 (127)	0.37
HbA_{1c} (%)	8.3 (1.1)	8.6 (1.1)	<0.001
UACR (mg/g)	88.8 (337.1)	260.7 (666.0)	<0.001
eGFR ($mL/min/1.73\ m^2$)	91.8 (27.3)	84.8 (23.4)	<0.001

Continuous data are presented as the mean (SD) and categorical data as indicated. At 1 year, HbA_{1c} values of 6.4% and 7.5% were achieved in intensive and standard groups, respectively, and remained relatively stable thereafter. eGFR was calculated from the four-variable MDRD Study equation. BP, blood pressure. †Smoker: smoked >100 cigarettes during lifetime.

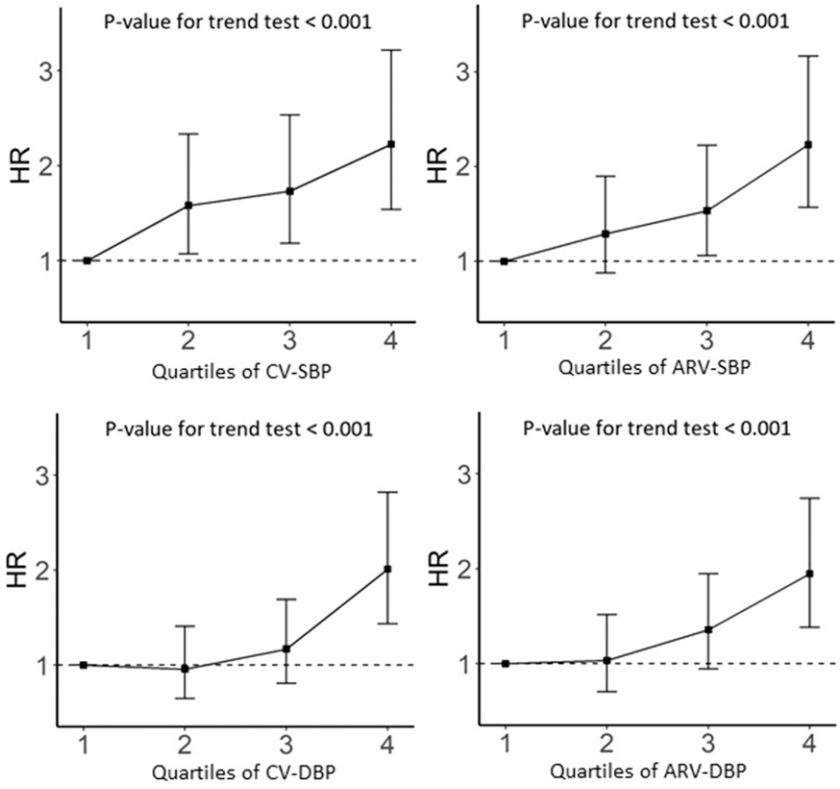

Figure 1—HR estimates for the risk of HF by quartiles of blood pressure variability in ACCORD. CV and ARV of blood pressure, adjusted for age, are shown for SBP in the top panel and DBP in lower panel. Results of trend tests are presented as text annotation in the figure.

In a series of sensitivity analyses, we addressed whether the associations could be driven in part by use of antihypertensive medications. Blood pressure variability in SBP and DBP was significantly greater in the groups with high antihypertensive use at the end of year 1 (i.e., use of two to three or four or more medications) than in the group with use of zero to one medications ($P < 0.001$ for CV and ARV); however, the association between blood pressure variability and HF was not stronger in those with more medication use. There were no major differences in percentages of antihypertensive medication use per category at years 1, 2, and 3, nor was the association between variability and HF markedly different if we instead analyzed the population beginning at year 1.

We also examined the effects of blood pressure variability stratified by participation in the blood pressure trial arms and observed that the relationship of SBP and DBP variability (CV and ARV) with incident HF was not just limited to those participating in the blood pressure trial (Supplementary Table 1). Furthermore, participants in the ACCORD blood pressure trial were highly adherent (>93%) to their trial medications (defined as taking 80–100% of their trial medications at each visit), and adjusting for medication adherence among those in the blood pressure arms did not noticeably influence the results. We did not see major differences in the results when stratifying by sex. Moreover, adjusting for randomization to the glucose or blood pressure treatment arms of ACCORD had negligible effects on the results.

Blood Pressure Variability and HF in the VADT

In the VADT, age, race, diabetes duration, history of CVD, pack-years of smoking, SBP, HDL cholesterol, triglycerides, UACR, and eGFR differed significantly between those who did and did not develop a new HF event (Supplementary Table 2). The associations between DBP variability measures and HF (Supplementary Table 3) were consistent with the ACCORD findings (model 3: CV-DBP HR 1.09, 95% CI 1.00–1.14, $P = 0.04$; ARV-DBP HR 1.16, 95% CI 1.06–1.27, $P = 0.002$). The elevated HRs for the SBP variability and HF association

Table 2—HRs for the association of blood pressure variables with HF estimated by Cox proportional hazards model in ACCORD (n = 9,383)

	Model 1		Model 2		Model 3	
	Age adjustment		Multivariate adjustment		Model 2 + cumulative mean BP	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cumulative mean SBP	1.03 (1.02–1.04)	**<0.001**	1.02 (1.01–1.04)	**0.001**	—	—
Cumulative maximum SBP	1.25 (1.19–1.32)	**<0.001**	1.22 (1.07–1.38)	**0.002**	1.09 (0.90–1.31)	0.37
CV-SBP	1.24 (1.13–1.35)	**<0.001**	1.15 (1.04–1.28)	**0.009**	1.15 (1.03–1.29)	**0.01**
ARV-SBP	1.26 (1.16–1.37)	**<0.001**	1.18 (1.06–1.30)	**0.002**	1.19 (1.07–1.32)	**0.001**
Cumulative mean DBP	0.99 (0.97–1.00)	0.13	1.00 (0.97–1.03)	0.90	—	—
Cumulative maximum DBP	1.03 (0.92–1.15)	0.63	1.07 (0.93–1.24)	0.35	—	—
CV-DBP	1.27 (1.17–1.38)	**<0.001**	1.18 (1.06–1.31)	**0.003**	1.18 (1.06–1.32)	**0.003**
ARV-DBP	1.24 (1.15–1.34)	**<0.001**	1.18 (1.06–1.31)	**0.002**	1.18 (1.06–1.31)	**0.002**

HRs (95% CI) and *P* values estimated by Cox proportional hazards model in ACCORD. Those with a history of HF at baseline were excluded. Blood pressure variables that were significant in age-adjusted models (model 1) were further adjusted for baseline factors that showed significant associations in Table 1 (model 2). In model 3, models were additionally adjusted for cumulative mean of blood pressure (BP). Model 3 was not computed if the model 2 HR was not statistically significant. *P* values <0.05 (bold) are considered significant.

were not statistically significant. When excluding the small number of women in the VADT, we did not see major differences in the results. Of note, there was an inverse association with both maximum SBP (HR 0.92) and maximum DBP (HR 0.81) in the fully adjusted models ($P < 0.001$), suggesting higher HF risk in those with lower blood pressure.

Blood Pressure Variability and HF in the Setting of Lower Blood Pressure in ACCORD

Because of insufficient statistical power for stratified analyses in the VADT, the effect of blood pressure variability by categories of baseline blood pressure was examined in ACCORD only. The age-adjusted risk for HF increased for CV-SBP, ARV-SBP, and CV-DBP with stepwise declines in baseline blood pressure, as displayed in Fig. 2 (e.g., for CV-SBP in model 1, those with baseline SBP ≥140, <140, <130, and <120 mmHg had HRs of 1.03, $P = 0.67$; 1.21, $P = 0.002$; 1.50, $P < 0.001$; and 1.69, $P < 0.001$, respectively). When mean blood pressure during the study, rather than baseline blood pressure, was used to divide the groups, there was a similar pattern of greater risk of HF with increased blood pressure variability in those with lower mean blood pressure. Although we examined low SBP and DBP separately, we recognize that there is extensive overlap between those with low baseline SBP and DBP. In fact, >80% of individuals with lower DBP (<70 mmHg) also had SBP <140 mmHg. When considering those with and without CVD history in the groups with low baseline blood pressure (DBP <70 mmHg and SBP <140 mmHg), the highest risk for blood pressure variability measures was seen among those with a history of CVD, whereas the associations were not significant in those without a CVD history (Supplementary Table 4). To explore the possibility that this may be related to cardiac ischemia, we tested whether blood pressure variability in progressively lower levels of blood pressure is also associated with development of a nonfatal MI. Interestingly, we saw similar trends as in the analysis for HF (e.g., CV-SBP for nonfatal MI in those with baseline SBP >140 mmHg, compared with those with SBP <120 mmHg, increases from HR 1.06, $P = 0.36$ to HR 1.36, $P = 0.0009$). Risk of MI associated with CV-DBP across strata of blood pressure showed a similar pattern.

Finally, to examine whether the direction of blood pressure variability may influence outcomes, we determined whether variability above the mean cumulative SBP or DBP or variability below the mean cumulative SBP or DBP was more associated with risk of HF in the fully adjusted model 3. We observed that variability area under the mean ($P = 0.03$ for SBP and $P < 0.001$ for DBP) but not variability area above the mean ($P = 0.92$ for SBP and $P = 0.17$ for DBP) represented a significant risk for HF.

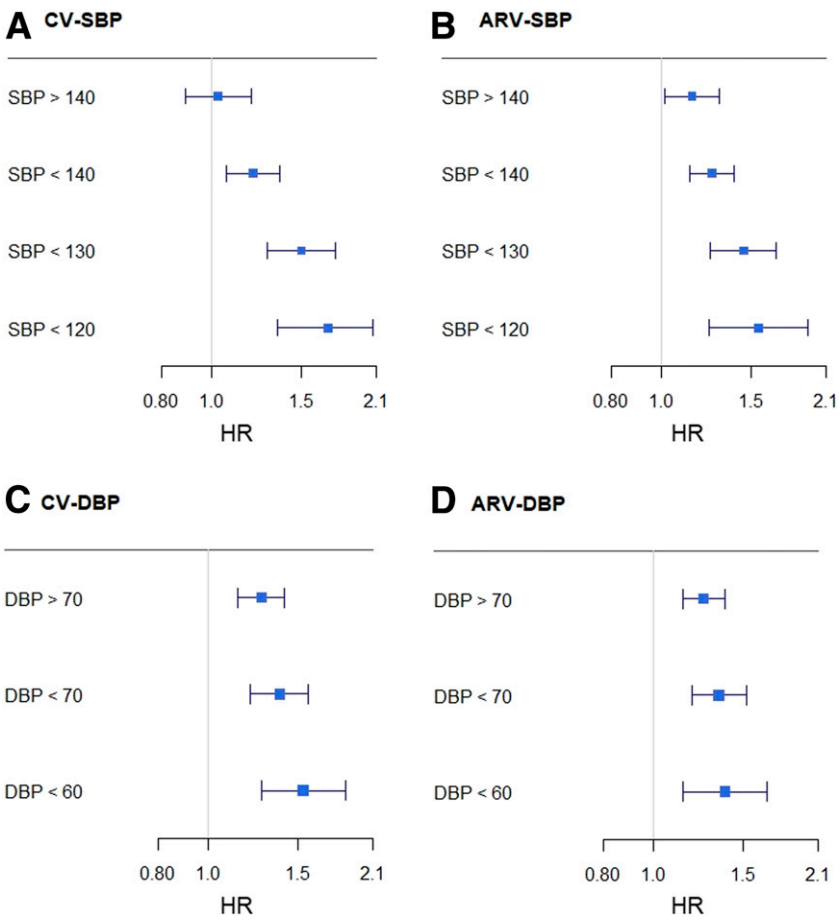

Figure 2—Associations of visit-to-visit systolic and diastolic variability with risk of HF, with HR estimates, by baseline blood pressure categories in ACCORD. *A*: CV-SBP by baseline SBP categories. *B*: ARV-SBP by baseline SBP categories. *C*: CV-DBP by baseline DBP categories. *D*: ARV-DBP by baseline DBP categories.

CONCLUSIONS

There is substantial evidence that HF represents an increasing burden in those with type 2 diabetes (19). While elevated blood pressure is appreciated as one of several cardiovascular risk factors for type 2 diabetes (20), it is essential to clarify the impact of blood pressure variability in those with type 2 diabetes (21). In this study, we demonstrate that blood pressure variability is a significant and robust predictor of HF using two large cohorts of patients with type 2 diabetes who had participated in clinical trials of glucose and other cardiovascular risk factor management. We showed that these relationships were present even in the setting of well-controlled management of other type 2 diabetes risk factors and in those undergoing additional blood pressure-lowering treatment. Importantly, the association of DBP variability and HF persisted after adjustment for overall levels of blood pressure in both cohorts and was strongest in those with lower baseline (or on study) blood pressure in ACCORD. These findings may support use of relatively easily accessible visit-to-visit blood pressure variability assessments to improve risk factor

stratification and further individualization of blood pressure treatment strategies.

Prior studies have reported associations of blood pressure variability and adverse cardiovascular outcomes, including stroke (22), MI (3), and mortality (1). More recent studies also indicated associations between blood pressure variability and HF. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) investigation of antihypertensive control, SBP and DBP variability were both associated with a 25% increase in the risk of HF (highest vs. lowest quintile of SD); this, however, was not significant in the fully adjusted model (5). The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial indicated greater risk of HF and death due to HF in those with increased blood pressure variability (7). In both trials, more than a third of participants reported having diabetes, suggesting this relationship could be relevant in both patients with and without diabetes.

The current study builds on this previous work in several ways. We report the association of SBP and DBP variability with HF in two large cohorts of individuals with type 2 diabetes, a population at very high risk for HF. These associations were sufficiently robust in ACCORD to persist after adjustment for baseline differences (including CVD history) between those who do or do not develop HF (model 2) and further adjustment for cumulative mean blood pressure or pulse pressure. This pattern held for DBP but not SBP variability in the VADT, possibly due to the smaller cohort size. In addition, these associations do not appear to be explained by use of and adherence to antihypertensive medications or enrollment in the blood pressure-lowering trial, as demonstrated in sensitivity analyses in ACCORD.

We found in ACCORD that increased variability in those with lower baseline blood pressures conferred an increased risk of HF in a nearly stepwise fashion. Although using a different end point (total cardiovascular events), the VALUE trial also found that associations of blood pressure variability with this outcome were stronger in patients with lower baseline SBP (7). There is recent evidence emphasizing that individuals with DBP in the low normal or less than low normal range may be at higher risk of CVD. Anderson et al. (23) reported in the VADT that even with SBP in range of guideline targets, baseline DBP $<$70 mmHg in asymptomatic individuals with type 2 diabetes was associated with increased CVD risk. Similarly, McEvoy et al. (12) found in the Atherosclerosis Risk in Communities (ARIC) community study that low DBP in otherwise healthy individuals was associated in a stepwise manner with increased risk for future myocardial damage as estimated by elevations in high-sensitivity cardiac troponin-T concentrations. However, it is important to note that recent blood pressure-lowering trials (14,24) found that lower blood pressure treatment targets conferred decreased (or no) risk for HF. As our data suggest greater potential impact of blood pressure variability in the lower blood pressure range, one interpretation of the data in aggregate is that reducing variability could enhance the benefits of blood pressure lowering, particularly at lower blood pressure target levels.

Several mechanisms have been put forward to account for the association between visit-to-visit blood pressure variability and adverse cardiovascular outcomes. These include decreased endothelial function (25) as well as increased arterial stiffness. Importantly, arterial stiffness was found to correlate with variability of SBP and DBP in a study of participants with untreated hypertension (26). Similarly, others reported decreased aortic distensibility with increased blood pressure variability in the Multi-Ethnic Study of Atherosclerosis (MESA) community cohort (27). Because both endothelial dysfunction and arterial stiffness have been implicated in the development of CVD, they could also be plausible contributors to the development of HF. However, it is unlikely that these two processes would be most prominent in the low blood pressure setting, nor did our results suggest that the association of blood pressure variability and HF was confined to those with high pulse pressure—a relatively good indicator of arterial stiffness (28). An additional possibility is that blood pressure variability may more directly increase the risk for myocardial ischemia. As coronary blood flow peaks during diastole, repeated transient declines in DBP over time may put cardiac tissue at increased risk of relative hypoperfusion. Our analysis showing an increasing level of risk from higher blood pressure variability for nonfatal MI with progressively lower levels of blood pressure provides further support for this hypothesis.

Although our study finds the risk for HF with higher blood pressure variability is increased in those with either low SBP or DBP, these lower pressures occur in the same individuals. Thus, our findings are still consistent with the notion that blood pressure variation may exacerbate effects of low DBP. This concept is also supported by our findings that *1*) DBP variability was more consistently and robustly associated with incident HF than SBP variability, *2*) that this association was strongest in those also with low baseline or on-trial DBP, and *3*) downward but not upward changes in blood pressure were related to risk for HF. It could be further anticipated that underlying atherosclerotic disease may exacerbate the adverse effect of higher blood pressure variability in the setting of low blood pressure, as suggested by our finding of a more prominent effect in those with a CVD history and low DBP.

Although substantial attention has been paid to SBP and DBP lowering, recent antihypertensive guidelines have begun to consider implications of low blood pressure management in apparently healthy individuals. As noted in the 2017 position statement of the American Diabetes Association (29), treatment recommendations for SBP among older adults ought to be tempered by accumulating evidence that accompanying reductions in DBP may lead to unfavorable outcomes. Our results provide additional clinically relevant information to this notion, indicating that DBP variability in those with low baseline DBP may be particularly deleterious. However, as noted above, results from both ACCORD (14) and the Systolic Blood Pressure Intervention Trial (SPRINT) (24) did not suggest that lowering blood pressure per se in those already with elevated blood pressures led to a higher incidence of HF. Thus, our data do not alter conclusions arising from these trials. It will be informative, however, to reexamine whether outcomes in blood pressure studies such as these appear modulated by restraining the extent of blood pressure variability. More detailed studies clarifying the role of blood pressure variability, and the relevant mechanisms,

in development of HF are clearly needed to help refine our understanding of and guidance for optimal blood pressure management.

Strengths of the current study include use of two large randomized clinical trials that included large numbers of blood pressure measures, long-term follow-up, and careful and blinded adjudication of HF events. We were also able in ACCORD to account for key medication factors, including use of and adherence to antihypertensive therapies that have been hypothesized to influence variability. Moreover, use of time-dependent estimates in our Cox model has some advantages over "landmark period" approaches commonly used in other observational studies of blood pressure variability. For example, use of time-dependent estimates permits inclusion of all blood pressure measures up until the HF event (30), which will presumably more accurately quantify blood pressure variation. The landmark approach also assumes that variation captured in the initial landmark period of the study will reflect variation during the subsequent observational period of the study.

We also note some limitations of the study. While the older, relatively homogenous patient populations in the VADT and ACCORD are at high risk for HF, the external validity of the current post hoc results may be limited and will require validation in other cohorts. The ACCORD population was extremely adherent to their medications, tempering our ability to test nuances in medication adherence in this context. The small numbers of HF events in the VADT precluded conducting stratified analyses as in ACCORD.

In conclusion, this study finds associations between visit-to-visit blood pressure variability and HF within ACCORD and the VADT. The associations in ACCORD persisted for both SBP and DBP variability and in the VADT for DBP variability when accounting for overall blood pressure control. Our study adds to the current literature that links blood pressure variability with adverse cardiovascular outcomes in those with type 2 diabetes (21) and provides additional evidence for an association of blood pressure variability with HF risk in diabetes. The novel finding that the association was stronger in those with low baseline blood pressures merits inquiry in future studies and may assist efforts to better individualize blood pressure strategies to maximize benefits while limiting harm.

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